

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 2 of 15

### **Amendments to the Claims**

This listing of claims will replace all prior versions, and listing, of claims in the application.

### **Listing of Claims:**

1-17. Cancelled

18 (Previously presented). A method of eliciting an immune response treating herpetic stromal keratitis in a mammal, the method comprising administering to the mammal an effective amount of a mutated herpesvirus in a pharmaceutically acceptable carrier, the herpesvirus having a mutation in one or more genes encoding a protein essential for viral genome replication to render the herpesvirus replication defective, said mutant herpesvirus having an ability to effect an antibody subclass shift of IgG2a/IgG upon *in vivo* administration to said mammal.

19 (Original). The method of claim 18 wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, CMV, HHV-6 or HHV-7.

20 (Original). The method of claim 19 wherein the herpesvirus is HSV-1 or HSV-2.

21 (Original). The method of claim 20 wherein the mutation is in the gene or genes encoding the proteins ICP8 or ICP 27.

22-30. Cancelled

31 (Previously presented). A composition in a pharmaceutically accepted carrier comprising:

a mutated herpesvirus characterized by a mutation in at least one gene encoding a protein essential for viral genome replication of said herpesvirus, thereby, rendering the virus genome replication defective; and,

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 3 of 15

the herpesvirus comprising one or more heterologous genes; wherein,  
the mutated herpesvirus is capable of infecting a mammalian cell and of eliciting  
an immune response to heterologous gene products in a mammal treated with the  
herpesvirus.

32-35. Cancelled

36 (Previously presented). A composition comprising a mutated herpesvirus capable  
of infecting a mammalian cell;

said herpesvirus comprising a mutation in one or more early genes encoding a  
protein essential for viral genome replication to render the herpesvirus replication  
defective; and,

said herpesvirus comprising one or more heterologous genes encoding  
heterologous gene products; wherein,

the mutated herpesvirus is capable of infecting a mammalian cell and of eliciting  
an immune response to the heterologous gene products in a mammal treated with said  
herpesvirus.

37-40. Cancelled

41 (Currently amended). A method of inducing an immune response ~~against~~  
herpesvirus in a mammal ~~against immunogen, the method comprising administering to said~~  
mammal an immune response inducing effective amount of an immunogenic composition  
vaccine-comprising a mutated herpesvirus in a pharmaceutically accepted carrier, said  
herpesvirus having a mutation in one or more genes encoding a protein essential for viral  
genome replication to render the herpesvirus replication defective, ~~and said herpesvirus further~~  
comprising encoding one or more heterologous genes encoding said immunogen.

42-64. Cancelled

Applicant: KNIPE et al.  
Serial No.: 08/278.601  
Page 4 of 15

65 (Currently amended). ~~The immunogenic composition of claim 50~~ An immunogenic composition comprising a pharmaceutically acceptable carrier and a mutated herpesvirus capable of infecting a mammalian cell and of eliciting an immune response in a mammal immunized with the composition, wherein the herpesvirus includes two or more mutations, at least one of the mutations being in the genes encoding HSV-1, ICP27; or HSV-1, ICP8; or in a corresponding early gene in a non-HSV-1 herpesvirus, and the mutation renders the herpesvirus incapable of replication, wherein one mutation is a deletion mutation and the other mutation is a nonsense mutation.

66 -67. Cancelled.

68 (Currently amended). An immunogenic composition comprising a pharmaceutically acceptable carrier and a replication defective herpesvirus which expresses a heterologous protein to which an immune response is desired, wherein said herpesvirus is characterized by a mutation in at least one gene encoding HSV-1, ICP27; or HSV-1, ICP8; or in a corresponding early gene in a non-HSV-1 herpesvirus, and the mutation renders the herpesvirus incapable of replication.

69 (Previously presented). The immunogenic composition of claim 68, wherein the herpesvirus is HSV-1, HSV-2, VZV, EBV, HHV-6 or HHV-7.

70. Cancelled.

71 (Previously presented). The immunogenic composition of claim 68 wherein the gene is HSV-1 ICP-27.

72 (Previously presented). The immunogenic composition of claim 68 wherein said gene is HSV-1 or HSV-2 ICP-8.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 5 of 15

73 (Previously presented). The immunogenic composition of claim 68, wherein said herpesvirus is characterized by a mutation in two or more genes encoding HSV-1, ICP27; or IISV-1, ICP8; or in a corresponding early gene in a non-HSV-1 herpesvirus, and the mutation renders the herpesvirus incapable of replication.

74. Cancelled.

75 (Previously presented). The immunogenic composition of claim 73, wherein said genes encode ICP8 and ICP 27.

76 (Previously presented). The immunogenic composition of claim 68, wherein the gene encoding ICP27 comprises a first mutation and the gene encoding ICP8 comprises a second mutation, thereby, the herpesvirus expressing the heterologous protein is rendered incapable of replication.

77 (Previously presented). The immunogenic composition of claim 73, wherein the gene encoding ICP27 comprises a first mutation, thereby, the herpesvirus expressing the heterologous protein is rendered incapable of replication.

78 (Previously presented). The immunogenic composition of claim 73, wherein the gene encoding ICP8 comprises a first mutation, thereby, the herpesvirus expressing the heterologous protein is rendered incapable of replication.

79 (Previously presented). The immunogenic composition of claim 73, wherein the herpesvirus expressing the heterologous protein is HSV-1 or HSV-2.

80 (Previously presented). The immunogenic composition of claim 79, wherein the heterologous protein is an immunogenic protein from a virus, bacteria, fungi or parasite.

81-82. Cancelled.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 6 of 15

83 (Currently amended). The immunogenic composition of claim 80, 82, wherein the immunogenic protein elicits a B- and/or T-cell immune response.

84 (Previously presented). A method of eliciting an immune response in a mammal, the method comprising administering to the mammal an immunogenic composition comprising a mutated herpesvirus, expressing a heterologous protein and is capable of infecting a mammalian cell and eliciting an immune response, wherein the herpesvirus includes a mutation in a gene encoding HSV-1, ICP27; or HSV-1, ICP8; or in a corresponding early gene in a non-HSV-1 herpesvirus, and the mutated herpesvirus is rendered incapable of replication.

85 (Previously presented). The method of claim 84, wherein the herpesvirus expressing the heterologous protein is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

86 (Previously presented). The method of claim 84, wherein the herpesvirus expressing the heterologous protein is HSV-1 or HSV-2.

87 (Previously presented). The method of claim 84, wherein the gene encoding ICP27 comprises a first mutation and the gene encoding ICP8 comprises a second mutation, thereby, the herpesvirus expressing the heterologous protein is rendered incapable of replication.

88 (Currently amended). The immunogenic composition of claim 68, 84, wherein the heterologous protein is an immunogenic protein from a virus, bacteria, fungi or parasite.

89 (Currently amended). The immunogenic composition of claim 88, 84, further comprising a mutation in at least two of the genes.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 7 of 15

90 (Currently amended). The immunogenic composition of claim 88 84, further comprising a mutation in at least two of the genes, wherein one mutation is a deletion mutation and the other mutation is a nonsense mutation.

91 (Previously presented). A method of treating a mammal to elicit an immunogenic response, the method comprising administering to the mammal an effective amount of an immunogenic composition comprising a mutated herpesvirus expressing a heterologous protein in a pharmaceutically acceptable carrier, wherein the herpesvirus includes a mutation in a gene encoding HSV-1, ICP27; or HSV-1, ICP8; or in a corresponding early gene in a non-HSV-1 herpesvirus, thereby, the mutated herpesvirus is rendered incapable of replication, and the mutant herpesvirus induces an immunogenic effect upon *in vivo* administration to the mammal.

92 (Previously presented). The method according to claim 91, wherein the herpesvirus contains a mutation in at least two of the genes and expresses a heterologous protein.

93 (Previously presented). The method according to claim 91, wherein the herpesvirus contains a mutation in at least two of the genes, wherein one mutation is a deletion mutation and the other mutation is a nonsense mutation.

94 (Previously presented). The method according to claim 91, wherein the herpesvirus contains at least two mutations in the genes.

95 (Previously presented). The method according to claim 94, wherein one mutation is a deletion mutation and the other mutation is a nonsense mutation.

96 (Previously presented). The method of claim 91, wherein the heterologous protein is an immunogenic protein from a virus, bacteria, fungi or parasite.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 8 of 15

97 (Previously presented). The method according to claim 91, wherein the *in vivo* immunogenic effect in a mammal comprises a B- cell and/or T cell response.

98 (Cancelled).

99 (Previously presented). The immunogenic composition of claim 104, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

100 (Previously presented). The immunogenic composition of claim 104, wherein the herpesvirus is HSV-1 or HSV-2.

101 (Previously presented). The immunogenic composition of claim 99, wherein a gene encoding ICP27 comprises a nonsense mutation and a gene encoding ICP8 comprises a deletion mutation.

102 (Cancelled).

103 (Cancelled).

104 (Currently amended). An immunogenic composition comprising a pharmaceutically acceptable carrier and a mutated herpesvirus capable of infecting a mammalian cell and of eliciting an immune response in a mammal immunized with the composition, wherein the herpesvirus includes two or more mutations, at least one of the mutations being in one or more genes encoding a protein essential for viral genome replication to render the herpesvirus incapable of replication, wherein one mutation is a nonsense mutation and another mutation is a deletion mutation.

105-108. Cancelled.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 9 of 15

109 (New). An immunogenic composition comprising a pharmaceutically acceptable carrier and a mutated replication defective herpesvirus capable of infecting a mammalian cell and of eliciting an immune response in a mammal immunized with the composition, wherein the herpesvirus includes two or more mutations in one or more genes, thereby rendering the herpesvirus to be viral genome replication defective.

110 (New). The immunogenic composition of claim 109, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

111 (New). The immunogenic composition of claim 109, wherein one mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus.

112 (New). The immunogenic composition of claim 109, wherein one mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

113 (New). The immunogenic composition of claim 109, wherein each of two mutations independently render the herpesvirus to be viral genome replication defective.

114 (New). An immunogenic composition comprising a pharmaceutically acceptable carrier and a mutated replication defective herpesvirus capable of infecting a mammalian cell and of eliciting an immune response in a mammal immunized with the composition, wherein the herpesvirus includes two or more deletion mutations in one or more genes, thereby rendering the herpesvirus to be viral genome replication defective.

115 (New). The immunogenic composition of claim 114, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

116 (New). The immunogenic composition of claim 114, wherein one deletion mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus.



Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 10 of 15

117 (New). The immunogenic composition of claim 114, wherein one deletion mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

118 (New). The immunogenic composition of claim 114, wherein each of two mutations independently render the herpesvirus to be viral genome replication defective.

119 (New). A method of eliciting an immune response in a mammal, the method comprising administering to the mammal an immunogenic composition comprising a mutated herpesvirus capable of infecting a mammalian cell and eliciting an immune response, wherein the herpesvirus includes two or more mutations in one or more genes, thereby rendering the herpesvirus to be viral genome replication defective.

120 (New). The method of claim 119, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

121 (New). The method of claim 119, wherein one mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus.

122 (New). The method of claim 119, wherein one mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

123 (New). The method of claim 119, wherein each of two mutations independently render the herpesvirus to be viral genome replication defective.

124 (New). A method of eliciting an immune response in a mammal, the method comprising administering to the mammal an immunogenic composition comprising a mutated herpesvirus capable of infecting a mammalian cell and eliciting an immune response, wherein the herpesvirus includes two or more deletion mutations in one or more genes, thereby rendering the herpesvirus to be viral genome replication defective.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 11 of 15

125 (New). The method of claim 124, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

126 (New). The method of claim 124, wherein one deletion mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus.

127 (New). The method of claim 124, wherein one deletion mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

128 (New). The method of claim 124, wherein each of two mutations independently render the herpesvirus to be viral genome replication defective.

129 (New). An immunogenic composition comprising a pharmaceutically acceptable carrier and a mutated replication defective herpesvirus capable of infecting a mammalian cell and of eliciting an immune response in a mammal immunized with the composition, wherein the herpesvirus includes two or more mutations, at least one of the mutations being in a gene encoding HSV-1, ICP27 or HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus, thereby rendering the herpesvirus to be viral genome replication defective.

130 (New). The immunogenic composition of claim 129, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

131 (New). The immunogenic composition of claim 129, wherein one mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus.

132 (New). The immunogenic composition of claim 129, wherein one mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

133 (New). The immunogenic composition of claim 129, wherein each of two mutations independently render the herpesvirus to be viral genome replication defective.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 12 of 15

134 (New). An immunogenic composition comprising a pharmaceutically acceptable carrier and a mutated replication defective herpesvirus capable of infecting a mammalian cell and of eliciting an immune response in a mammal immunized with the composition, wherein the herpesvirus includes two or more deletion mutations, at least one of the deletion mutations being in a gene encoding IHSV-1, ICP27 or HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus, thereby rendering the herpesvirus to be viral genome replication defective.

135 (New). The immunogenic composition of claim 134, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

136 (New). The immunogenic composition of claim 134, wherein one deletion mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-IHSV-1 herpesvirus.

137 (New). The immunogenic composition of claim 134, wherein one deletion mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

138 (New). The immunogenic composition of claim 134, wherein each of two mutations independent

139 (New). A method of eliciting an immune response in a mammal, the method comprising administering to the mammal an immunogenic composition comprising a mutated herpesvirus capable of infecting a mammalian cell and eliciting an immune response, wherein the herpesvirus includes two or more mutations, at least one of the mutations being in a gene encoding HSV-1, ICP27 or HSV-1, ICP8 or in a corresponding early gene in a non-IHSV-1 herpesvirus, thereby rendering the herpesvirus to be viral genome replication defective.

140 (New). The method of claim 139, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

Applicant: KNIPE et al.  
Serial No.: 08/278,601  
Page 13 of 15

141 (New). The method of claim 139, wherein one mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus.

142 (New). The method of claim 139, wherein one mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

143 (New). The method of claim 139, wherein each of two mutations independently render the herpesvirus to be viral genome replication defective.

144 (New). A method of eliciting an immune response in a mammal, the method comprising administering to the mammal an immunogenic composition comprising a mutated herpesvirus capable of infecting a mammalian cell and eliciting an immune response, wherein the herpesvirus includes two or more deletion mutations, at least one of the deletion mutations being in a gene encoding HSV-1, ICP27 or HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus, thereby rendering the herpesvirus to be viral genome replication defective.

145 (New). The method of claim 144, wherein the herpesvirus is selected from the group consisting of HSV-1, HSV-2, VZV, EBV, HHV-6 and HHV-7.

146 (New). The method of claim 144, wherein one deletion mutation is in the gene for encoding HSV-1, ICP8 or in a corresponding early gene in a non-HSV-1 herpesvirus.

147 (New). The method of claim 144, wherein one deletion mutation is in the gene for encoding HSV-1, ICP27 or in a corresponding early gene in a non-HSV-1 herpesvirus.

148 (New). The method of claim 144, wherein each of two mutations independently render the herpesvirus to be viral genome replication defective.